STUDY OF LIVER FUNCTION ABNORMALITIES IN THE TUBERCULOSIS PATIENTS UNDERGOING RNTCP-DOTS IN TB CLINIC MADURAI

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MADURAI MEDICAL COLLEGE, MADURAI.

CERTIFICATE

This is to certify that this dissertation titled "**STUDY OF LIVER FUNCTION ABNORMALITIES IN THE TUBERCULOSIS PATIENTS UNDERGOING RNTCP-DOTS IN TB CLINIC MADURAI** submitted by **DR. C. THOMAS KINGSLEY** to the faculty of General Medicine, **The Tamil Nadu Dr. M.G.R. Medical University, Chennai** in partial fulfillment of the requirement for the award of MD degree branch I General Medicine, is a bonafide research work carried out by him under our direct supervision and guidance.

DR. M. MUTHIAH, M.D.
Professor of Medicine,
Chief, VI Medical Unit,
Department of Medicine,
Madurai Medical College,
Madurai.

DR.A.AYYAPPAN, M.D.
Professor and Head,
Department of Medicine,
Madurai Medical College,
Madurai.

DECLARATION

I**, Dr.C.Thomas Kingsley,** solemnly declare that the dissertation titled "**Study of Liver Function Abnormalities in the tuberculosis Patients Undergoing RNTCP-DOTS in TB Clinic Madurai"** has been prepared by me.

This is submitted to **The Tamil Nadu Dr. M.G.R. Medical University, Chennai,** in partial fulfillment of the rules and regulations for the award of MD degree (branch I) General Medicine.

Place: Madurai

Date: **Dr.C.Thomas Kingsley.**

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CONTENTS

INTRODUCTION

Tuberculosis has proved to be a menace for the human population in general and to the developing countries in particular as a widely prevalent infectious disease. WHO has declared that Tuberculosis is a global emergency. An effective control has been achieved by the widespread use of anti tuberculosis drugs. However, despite their efficacy, superadded problems have to be faced in terms of long duration of treatment, emergence of MDR strains and certain adverse effects ascribed to these drugs. Among these adverse effects hepatotoxicity is a well known complication of Anti Tuberculous Therapy (ATT).

The severity ranges from alteration in liver enzymes, chronic active hepatitis and picture of acute hepatitis, occasionally complicated by acute liver failure carrying very high mortality unless transplanted. It is common with Isoniazid especially when given in combination with Rifampicin and Pyrazinamide. Fifteen to 20 percent of patients receiving Isoniazid as a single agent for prophylaxis against tuberculosis may have increased serum alanine and aspartate aminotransferase levels, but only one percent develop hepatic necrosis severe enough to require the withdrawal of the drug. The clinical, biochemical and histopathological features of drug induced hepatotoxicity (DIH) are indistinguishable from that of viral hepatitis.

Early identification and modification of treatment regimen are required for patients who are at increased risk of anti tuberculous drug induced hepatotoxicity and hence reducing the morbidity and mortality.

Reported risk factors for hepatotoxicity include: older age, female sex, poor nutritional status, high alcohol intake, pre-existing liver disease, HIV co-infection, hepatitis B carriage, increased prevalence of viral hepatitis in developing countries, hypoalbuminaemia, advanced tuberculosis, inappropriate use of drugs and acetylator status.

Despite the above known risk factors, there is a subset of patients who develop fulminant hepatic failure as an idiosyncratic reaction to isoniazid.

There has been an increase in the incidence of hepatotoxicity in the short course regimen followed by the RNTCP but exact incidence in our population is not known.

REVIEW OF LITERATURE

TUBERCULOSIS

DEFINITION

Tuberculosis is a bacterial infection caused by the acid fast bacillus Mycobacterium tuberculosis. The principal lesions are found in the lungs although other organs like lymph nodes, abdomen, meninges, bones and joints could be involved by dissemination. The major portal of entry is by droplet inhalation except in bovine tuberculosis where the organism enters by the oral route.

Tuberculosis affects humans in mainly two forms

Primary TB: is common among children and usually not transmissible

Secondary (postprimary) TB: happens in adults which is often infectious

PATHOGENESIS

This is determined by both the bacterial and host factors. The tubercle bacillus has three important factors which distinguish it from other organisms and help in the pathogenetic process:

1. Slow generation time
2. Lack of exotoxin or endotoxin
3. High lipid content of bacillus[1]

PHARMACOTHERAPY OF TUBERCULOSIS

For many years, the only drug used to treat tuberculosis was isoniazid and the duration of therapy was nearly 18 months. In 1972, Wallace fox and his colleagues showed that the addition of rifampicin, and pyrazinamide to regimens containing isoniazid made it possible to reduce the duration of treatment.

Advantages of the short course regimen include rapid bacteriological conversion, lower failure rates, better patient compliance and reduction in the frequency of emergence of drug resistant bacilli, the only disadvantage being the high cost.

There are now a number of short course regimens of six months duration which are highly effective, less toxic and well tolerated. The regimens used under the Revised National Tuberculosis Control Program (RNTCP) are shown in table 1.[2]

TABLE 1: CATEGORIES OF ATT UNDER RNTCP

Category	Type of patient	Regimen
Category I	New sputum positive Seriously ill** sputum negative Extra pulmonary seriously ill	$2(HRZE)_3 + 4(HR)_3$
Category II	Sputum positive default, failure and relapse,others***	$2(HRZES)_3+$ $1(HRZE)_3 + 5(HRE)_3$

Category III	Sputum negative not seriously ill Extra pulmonary not seriously ill	$2(HRZ)_3 + 4(HR)_3$

The numbers before the letters denote the number of months of treatment.

The subscript after the letters denotes number of doses per week.

The strengths of the drugs are as follows: isoniazid (H)-600mg, rifampicin(R)-450mg, Ethambutol (E)-1200mg, pyrazinamide (Z)-1500mg, streptomycin(S)-750mg.

Patients who weigh 60kg or more receive additional 150mg rifampicin.

Patients who are more than 50yrs receive 500mg streptomycin.

Patients who weigh < 30kg receive drugs as per body weight.

Patients in category I and II who remain sputum positive at the end of the intensive phase are given one more month of intensive therapy.

Patients in categories I and II who have positive sputum smear at the end of the initial intensive phase receive an additional month of intensive phase treatment.

** Seriously ill also includes, any patient, pulmonary or extra pulmonary who is HIV positive

***In exceptional cases, patients who are sputum smear negative or extra pulmonary can have relapse or failure and categorized as, “others”

Examples of extra pulmonary seriously ill include meningitis, pericarditis, disseminated tuberculosis, peritoneal, genitourinary tuberculosis and spinal tuberculosis

with neurological complications. [3]

CLASSIFICATION OF ANTITUBECULAR AGENTS

Traditionally anti TB agents have been classified into first line and second line agents as follows:

First line essential: isoniazid, rifampicin, pyrazinamide.

First line supplementary: ethambutol and streptomycin.

Second line: older agents (paraaminosalicylic acid, ethionamide and cycloserine), newer agent (rifapentine), kanamycin, amikacin, capreomycin and newer quinolones like gatifloxacin and moxifloxacin.[1]

TABLE 2: SIDE EFFECTS OF ANTI TB DRUGS

Isoniazid	Common	Anorexia, nausea, vomiting, fever
	Rare	Rash, peripheral neuropathy, hepatotoxicity, optic neuritis, hyperglycemia, hemolytic anemia
Rifampicin	Common	Orange coloration of urine, nausea, diarrhea, rash
	Rare	Hepatotoxicity, flu like syndrome (intermittent regimen), thrombocytopenia, interstitial nephritis, menstrual disturbances
Pyrazinamide	Common	Nausea, vomiting, fever
	Uncommon	Hepatitis, urticaria, skin rash, arthralgia
	Rare	Photosensitivity, gout, sideroblastic anemia, aggravation of peptic ulcer
Ethambutol	Common	Optic neuritis, arthralgia, color blindness
	Rare	Hepatitis, interstitial nephritis, cutaneous reaction

Streptomycin	Common	Vertigo, tinnitus, cutaneous hypersensitivity, deafness
	Rare	Renal damage, agranulocytopenia, aplastic anemia, neuromuscular blocking action[1]

ISONIAZID

Isoniazid is still considered the main drug in any anti TB regimen. Its primary mechanism of action is inhibition of synthesis of mycolic acids which are important constituents of the bacterial cell wall. 90% of the drug is excreted within 24 hours in the urine and the excretory products are mainly due to acetylation. The acetylation is significantly altered by the acetylator status of the individual. The status is measured by estimating free and total sulfa dimidine in blood and urine. Several risk factors for isoniazid toxicity have been identified which include acetylator status, old age, alcoholism and malnutrition. Jaundice occurs in 0.6% to 1% of patients whereas enzyme increase occurs in 10-20% of the patients.

RIFAMPICIN

Rifampicin inhibits DNA dependent RNA polymerase of mycobacterium. It is bactericidal for both intracellular and extra cellular organisms and is widely distributed in all body fluids including CSF. Hepatotoxicity from rifampicin rarely occurs in patients with normal liver function. Risk factors include old age, chronic liver disease and alcoholism. Increase in bilirubin and alkaline phosphatase are characteristic of rifampicin toxicity. Clinical hepatitis occurs in 0.6% to 2% whereas enzyme increase occurs in 5-10%. One Indian study shows an incidence of jaundice of 7-8%. Toxicity

appears to be enhanced by the addition of isoniazid.

PYRAZINAMIDE

It is a synthetic pyrazine derivative of nicotinamide. Target appears to be mycobacterial mycolic acid I gene which is involved in mycolic acid synthesis. When a dose of 40-50mg/kg is administered orally, hepatotoxicity is seen in 15% of patients and jaundice in 2-3%. Recent regimens are much safer as they employ lower doses. A large Indian study showed that in regimens containing isoniazid, rifampicin and pyrazinamide, there was no additional hepatoxicity contributed by pyrazinamide.

ETHAMBUTOL

It is a bacteriostatic drug with no reports of hepatotoxicity. Three fourths of the ingested dose is excreted unchanged through the kidneys.

BACTERIAL POPULATIONS AND ACTIONS OF DRUGS

A model proposed for explaining the early bactericidal and special sterilizing properties of drugs includes:

Population A: actively dividing organisms, killed mainly by INH.

Population B: semi dormant organisms mainly seen in acid pH inhibited by pyrazinamide.

Population C: semi dormant organisms with spurts of activity killed mainly by rifampicin.

Population D: completely dormant, unaffected by any drug.[1]

DRUG INDUCED LIVER INJURY

Drug-induced liver injury (DILI) has been a long-standing concern in the treatment of tuberculosis (TB) infection. The liver has a central role in drug metabolism and detoxification, and is consequently vulnerable to injury.[4]

Drug-induced liver injury (DILI) is ultimately a clinical diagnosis of exclusion. Other causes of liver injury, such as acute viral hepatitis, should be methodically sought and their absence makes the diagnosis plausible. Usually, the time of onset to acute injury is within months of initiating a drug. Rechallenge with the suspected offending agent with more than twofold serum alanine aminotransferase (ALT) elevation and discontinuation leading to a fall in ALT, is the strongest confirmation of the diagnosis. Rechallenge may, in some instances, endanger the patient and is usually confined to essential drugs or used when multiple potentially hepatotoxic drugs have been administered concomitantly.

DILI may result from direct toxicity of the primary compound, a metabolite, or from an immunologically mediated response, affecting hepatocytes, biliary epithelial cells and/or liver vasculature. In many cases, the exact mechanism and factors contributing to liver toxicity remain poorly understood.

The two major classes of DILI are the predictable and unpredictable responses. Predictable DILI is generally characterized by certain dose-related injury in experimental animal models, has a higher attack rate and tends to occur rapidly. Injurious free radicals cause hepatocyte necrosis in zones farthest from the hepatic

arterioles, where metabolism is greatest and antioxidant detoxifying capacity is the least.

Unpredictable or idiosyncratic reactions comprise most types of DILI. These hypersensitivity or metabolic reactions occur largely independent of dose and relatively rarely for each drug, and may result in hepatocellular injury and/or cholestasis. Hepatocyte necrosis is often distributed throughout hepatic lobules rather than being zonal, as is often seen with predictable DILI. In hypersensitivity reactions, immunogenic drug or its metabolites may be free or covalently bound to hepatic proteins, forming haptens or neoantigens. Antibody-dependent cytotoxic, T-cell and occasionally eosinophilic hypersensitivity responses may be evoked. Released tumor necrosis factor (TNF), interleukin (IL)-12 and IFN promote hepatocellular programmed cell death (apoptosis), an effect opposed by IL 4, IL-10, IL-13, and monocyte chemotactic protein-1.

Metabolic idiosyncratic reactions may result from genetic or acquired variations in drug biotransformation pathways, with synthesis or abnormally slow detoxification of a hepatotoxic metabolite. Metabolic idiosyncratic reactions may have a widely variable latent period, but recur within days to weeks after re-exposure.

Types of DILI

A variety of clinical syndromes may be seen with DILI, even with a single drug.[5]

Hepatic adaptation

Exposure to certain drugs may evoke physiologic adaptive responses. The induction of survival genes, including those that regulate antioxidant, anti-inflammatory

and antiapoptotic pathways, may attenuate toxin-related injurious responses. Such injury may also stimulate hepatocyte proliferation and protective adaptation. Asymptomatic, transient elevations of ALT may reflect slight, nonprogressive injury to hepatocyte mitochondria, cell membranes or other structures. Such injury rarely leads to inflammation, cell death or significant histopathologic changes. The induction of hepatic microsomal (cytochrome P450) enzymes, capable of metabolizing the inducing medication, is another form of hepatic adaptation.

Drug-induced acute hepatitis or hepatocellular injury

A transaminase threshold for clinicopathologically significant drug-induced hepatitis has not been systematically determined for most medications. Patients with acute hepatocellular injury may be asymptomatic or may report a prodrome of fever and constitutional symptoms, followed by nausea, vomiting, anorexia and lethargy. Histopathology may reveal focal hepatic necrosis, with bridging in severe cases. Markedly increased transaminase concentrations followed by jaundice imply severe liver disease with a 10% possibility of fulminant failure, as said by the late hepatologist and DILI expert Hyman Zimmerman. Coagulopathy may develop 24 to 36 hours after onset, although this can subsequently resolve. Coagulopathy persisting beyond 4 days is a poor prognostic sign in acetaminophen-related hepatotoxicity.

Nonalcoholic fatty liver disease

Steatosis or simple fatty liver is most commonly caused by obesity, insulin resistance and probably alterations in triglyceride metabolism. Ethanol, steroids and

highly active antiretroviral therapy (HAART) are associated with the development and exacerbation of non alcoholic fatty liver disease. Constitutional symptoms, nausea, vomiting or abdominal pain are uncommon. Laboratory findings in severe cases include hypoglycemia, increased serum transaminase concentrations, prolonged coagulation time and metabolic acidosis. Most instances of drug-induced steatosis are reversible, if the offending agent is stopped. Persistent steatotic injury may progress to steatohepatitis, characterized histopathologically by hepatic inflammation, fatty infiltration and by a subsequently higher risk of cirrhosis.

Granulomatous hepatitis

Granulomata are common, nonspecific findings in liver histology and are potentially related to infectious, inflammatory or neoplastic etiologies. Hypersensitivity reactions to drugs, such as allopurinol, quinidine, sulfonamides and pyrazinamide are a common cause of this type of lesion. Patients may have fever, lethargy, myalgias, rash, lymphadenopathy, hepatosplenomegaly with increased serum ALT concentration and even vasculitis.

Cholestasis

Bland cholestasis, typically reported with estrogen treatment, consists of asymptomatic, usually reversible increases in serum alkaline phosphatase and bilirubin concentration caused by a failure of bilirubin transport. There is a lack of inflammation in liver tissue.

Chemical cofactors for DILI

Ethanol induces cytochrome P450 2E1, which promotes metabolism of ethanol itself, acetaminophen and others. Ethanol metabolism yields acetaldehyde, which contributes to glutathione depletion, protein conjugation, free radical generation and lipid peroxidation. Chronic ethanol abuse activates hepatic collagen-producing sinusoidal (stellate) cells, potentially contributing to fibrosis.

Pre-existing liver disease

Abnormal baseline transaminases are an independent risk factor for DILI. Patients with HIV and hepatitis C however, appear to have increased frequency of antiretroviral medication related DILI. The severity of DILI, when it occurs, may be greater in patients with underlying liver disease, likely reflecting a summation of injuries.

Clinical syndromes associated with Drug induced hepatotoxicity include:

1. Liver enzyme elevation in asymptomatic patients
2. Acute viral hepatitis like picture
3. Fulminant hepatic failure
4. Sub acute hepatic failure
5. Cholestatic hepatitis
6. Acute hepatic venous outflow obstruction
7. Autoimmune hepatitis like picture
8. Chronic hepatitis
9. Cirrhosis.[6]

MECHANISM OF HEPATOTOXICITY DUE TO ANTI TB AGENTS

ISONIAZID

Reactive metabolites of MAH (mono acetyl hydrazine) are probably toxic to tissues through free radical generation. The antioxidant N-acetyl-cysteine, a substrate for glutathione synthesis, inhibits isoniazid-induced liver injury in pretreated rats, with unknown relevance in humans.

Additional metabolic idiosyncratic mechanisms appear to be operative. Slow acetylators appear to be particularly susceptible to hepatotoxicity. The isoniazid metabolite acetyl-hydrazine covalently binds to liver macromolecules, a process mediated by microsomal enzymes. The exact mechanism is still elusive.[1]

RIFAMPICIN

Conjugated hyperbilirubinemia probably is caused by rifampin inhibiting the major bile salt exporter pump. Asymptomatic elevation of bilirubin may also result from dose-dependent competition with bilirubin for clearance at the sinusoidal membrane or from impeded secretion at the canalicular level. Rare hepatocellular injury appears to be a hypersensitivity reaction and it may be more common with large, intermittent doses. Hypersensitivity reactions have been reported in combination with renal dysfunction, hemolytic anemia or flu like syndrome. Studies have proved that rifampicin induced hepatitis occurs earlier than isoniazid. There is also evidence that the addition of rifampicin to isoniazid causes enzyme induction and enhanced production of its toxic metabolites.

PYRAZINAMIDE

Pyrazinamide may exhibit dose dependent and idiosyncratic hepatotoxicity. Several decades ago, daily doses of pyrazinamide at 40 to 50 mg/kg commonly caused hepatotoxicity, and a relationship to dose was noted. There may be shared mechanisms of injury for isoniazid and pyrazinamide, because there is some similarity in molecular structure. Patients who previously had hepatotoxic reactions with isoniazid have had more severe reactions with rifampin and pyrazinamide given for latent tuberculosis infection. Pyrazinamide may induce hypersensitivity reactions with eosinophilia and liver injury or granulomatous hepatitis.

RIFABUTIN

At the usual doses (150-200 mg/day), hepatotoxicity is uncommon. There is less induction of hepatic microsomal enzymes than with rifampin. Elevated transaminases have been reported with high-dose (600 mg/day) rifabutin treatment in combination with macrolides.

HEPATOTOXICITY DURING TREATMENT OF TB

Overall, the risk of TB DILI in various studies ranges from 5% to as high as 33%. The possible risk factors for TB DILI are discussed subsequently.[5]

Age over 35

Several studies suggest that increasing age is a risk factor for TB DILI, but often statistical significance was not achieved or hepatotoxicity was not treatment limiting. One study reported a TB DILI rate ranging from 2 to 8% as age increased, with an

average of 5%.Other studies have reported that hepatotoxicity ranges from 22 to 33%in those older than 35 years, compared with 8 to 17% in those younger than 35 years.[7]

Children

There are varied reports of increased hepatotoxicity amongst children treated with anti TB therapy which was especially high in children with neurotuberculosis.[8]

Sex

For women, several studies report increased risk of hepatotoxicity, but this was not always treatment limiting, or did not achieve statistical significance. One study did show a four times higher risk of treatment limiting hepatotoxicity in women, but with an overall incidence of only 2%. Two other studies showed no increased risk in women.[9]

Cofactors

Several studies have indicated that alcohol use was a significant predictor of TB DILI, whereas two studies found no association.[10]

Abnormal Baseline Transaminases

One study found an increased risk of hepatotoxicity during treatment of TB disease in individuals with abnormal baseline transaminases.[11]

Acetylator Status

When acetylation rate has been determined by phenotypic assays, slow acetylators have experienced more hepatotoxicity in some studies but not in others.

Other Factors

Malnutrition or hypoalbuminemia was associated with TB DILI in several studies from India.[12] The presence of HLA-DQB1*0201 is an independent risk factor for the development of TB DILI.[13] Gene polymorphisms at loci of genes coding for cytochrome P4502E1 and for glutathione S-transferase have also been associated with hepatotoxicity.[14]

Disease severity

Extensive TB disease itself may be a risk factor for TB DILI, although confounding factors are impossible to exclude.[12] Liver transplant patients with TB appear to have a high rate of hepatotoxicity, with five of six treated patients developing this complication, confirmed by liver biopsy and three of six suffering graft rejection.

Regimen

In a meta-analysis, the presence of rifampicin in a multidrug treatment regimen increased the incidence of significant hepatotoxicity for adults from 1.6 to 2.55% and in children from 1.0 to 6.9%.[15] The influence of pyrazinamide on TB DILI is ambiguous; some studies indicate little to no increased rate of hepatotoxicity, whereas others point to it as a contributor to increased incidence or severity of hepatotoxicity, although dosing variations and patient selection biases may have contributed to these results.

HIV-infected Individuals

In a Western European clinical trial enrolling patients with TB-AIDS from 1989

to 1994, many who used intravenous drugs, 13 to 15% of patients had transaminase increases of at least three times the ULN in the first 2 months. Hepatoxicity was attributed to isoniazid in 55%of those with hepatitis. In a study of HIV, hepatitis C and TB treatment, HIV infection independently increased the risk fourfold of serum transaminase increase to 120 IU/L or of total bilirubin to at least 1.5 mg/dl. Approximately 27%of HIV infected individuals developed hepatotoxicity, compared with 12% among HIV-uninfected individuals. Nearly 80% of the patients in this study had a history of alcohol abuse, although random testing did not reveal active drinking, patients had not consumed alcohol in the 10 days before study entry, and all had normal baseline hepatic transaminases.[16]

Hepatitis B

Several studies from Asia have addressed DILI during treatment of TB disease in patients with hepatitis B infection. Additional studies are needed, but the limited data leave sufficient concern that hepatitis B maybe a risk factor for more frequent or severe hepatotoxicity during treatment of TB disease.

Hepatitis C

Hepatitis C was an independent risk factor for the development of hepatotoxicity, elevating the risk fivefold of transaminase elevation of at least 120 U/L, or of serum bilirubin of at least 1.5 mg/dl. Co infection with both hepatitis C and HIV elevated the risk of hepatotoxicity more than 14-fold.

DILI with Second-line Anti-TB Agents

Hepatotoxicity has been recognized to occur in about 2% of patients treated with ethionamide or prothionamide and in 0.3% of patients treated with para-aminosalicylic acid[17, 18]. Cycloserine does not appear to be associated with hepatotoxicity, but should be used with caution in patients at risk for alcohol withdrawal seizures.

Singh et al[19] reported an overall mortality of 12% in patients with ATT induced hepatotoxicity while it was 75% in patients with acute and sub acute liver failure.

In a case control study from AIIMS New Delhi, Pande et al[20] proposed the following diagnostic criteria for ATT induced hepatotoxicity-

1. Symptoms and signs of icteric hepatitis (anorexia, nausea, jaundice)
2. Rise in liver transaminases to more than 3 times the upper limit of normal on 3 occasions or a single value of >250IU/L.
3. Increase in serum bilirubin >1.5mg/dl
4. Absence of serological evidence of viral hepatitis.

In a retrospective study of 519 patients in Germany receiving isoniazid, rifampicin and pyrazinamide, hepatotoxicity was observed in 11% of patients[9].

In another study of 456 patients from Argentina receiving all 5 first line drugs, liver injury was seen in 9.9% of patients[21].

MANAGEMENT OF TB DILI

<u>Pretreatment Clinical Evaluation</u>

1. A standardized history form is recommended, which includes risk factors for hepatotoxicity.

2. The physical examination should include evaluation for signs of liver disease, such as liver tenderness, hepatosplenomegaly, jaundice, caput medusa, spider angiomata, ascites, and edema.

3. Previous laboratory values should be reviewed when available.

4. Screening for viral hepatitis should be considered for the following patients

- Individuals who inject drugs;
- were born in endemic areas of Asia, Africa, the Pacific Islands, Eastern Europe, or the Amazon Basin;
- are HIV infected;
- may have had sexual or household contact with chronically infected individuals;
- may have had occupational exposure to infected blood;
- are chronic hemodialysis patients;
- are recipients of clotting factors before 1987;
- have undiagnosed liver disease

5. Voluntary HIV counseling and testing are recommended for all patients with TB disease.[5]

Patient Education

1. Printed instructions should include clinic telephone numbers, include explicit instructions for after-hours care, and utilize patient preferred language at a readable level.

2. Patients should be categorically told to immediately stop medications for nausea,

vomiting, abdominal discomfort, or unexplained fatigue and to contact the clinic for further evaluation.

3. Patients should attend clinic follow-up visits for monitoring and reinforcement of education.

4. Patients should be warned about concomitant alcohol and hepatotoxic over-the-counter, and alternative and prescription medication use.

5. Patients should inform their health care providers of anti-TB medications prescribed drug adverse events.

Baseline laboratory testing and monitoring:

1. Baseline measurements of serum transaminases, bilirubin, alkaline phosphatase, creatinine and a blood platelet count are recommended for all adults beginning treatment for TB disease.

2. For patients with preexisting severe liver disease, some clinicians also recommend periodic measurement of prothrombin time and INR to assess hepatic synthetic function.

3. Routine measurements during treatment are recommended when baseline abnormalities are present and for patients, who chronically consume alcohol, take other potentially hepatotoxic medications or who have viral hepatitis or history of liver disease, HIV infection or prior TB DILI.

4. In patients with abnormal baseline transaminases, the range of their prior fluctuations may be of assistance in interpreting results of biochemical monitoring of treatment.

5. Some providers prefer to monitor ALT in women or older adults being treated for TB disease

7. ALT is preferred for detecting and tracking hepatocellular injury in those who develop symptoms of hepatotoxicity.

8. Measurements of AST, bilirubin and alkaline phosphatase are adjunctive for monitoring chronic liver disease, cholestasis or severe hepatocellular injury.

9. The ULN used should be that of the laboratory performing the assay.

10. Optimally, reference limits for enzymes should be adjusted for age in children and in adults older than 60 and for sex in adults, if available.

11. Hepatitis B surface antigen seropositive individuals with elevated ALT should have HBeAg testing. If positive, rifampin may be preferred over isoniazid. A hepatologist should be consulted regarding further testing and possible pretreatment in individuals with an ALT at least two times the ULN and who are HBeAg seropositive. In HBeAg-seropositive individuals, clinical and ALT monitoring should occur every 2 to 4 weeks.

12. Patients with baseline transaminases more than three times the ULN should have ALT retested along with bilirubin, as well as screening for viral or other causes of hepatitis, including alcohol and hepatotoxic drugs.

Treatment of TB Disease

Regimen selection

The crucial efficacy of isoniazid and particularly rifampin warrants their use and retention, if at all possible, even in the face of preexisting liver disease. Several regimens are recommended if baseline serum ALT is more than three times the ULN and TB is not believed to be the cause.

1. Treatment without pyrazinamide might utilize isoniazid and rifampin for 9 months with ethambutol until drug susceptibility testing of the M.tuberculosis isolate is completed.

2. In patients with cirrhosis, rifampin, Ethambutol and treatment with levofloxacin, moxifloxacin, gatifloxacin or cycloserine for 12 to 18 months may be considered.

3. For patients with encephalopathic liver disease, Ethambutol combined with a fluoroquinolone, cycloserine and capreomycin or aminoglycoside for 18 to 24 months may be an option. However, these regimens have not been tested systematically.

4. Some providers avoid aminoglycosides in severe, unstable liver disease due to concerns about renal insufficiency or bleeding from injected medication in patients with thrombocytopenia and/or coagulopathy.

Interventions for hepatotoxicity.

The first-line anti-TB drugs, especially rifampin, should not be discontinued for mild gastrointestinal complaints, which may be relatively frequent in the initial weeks of anti-TB treatment. If serum transaminase concentrations are more than five times the ULN (with or without symptoms)or more than three times the ULN with jaundice and/or hepatitis symptoms, then potentially hepatotoxic medications should be stopped

immediately and the patient evaluated promptly. Serologic tests for hepatitis A, B, C and E viruses should be obtained, and the patient should be evaluated for biliary disease, use of alcohol and other hepatotoxic drugs. Some experts recommend interrupting treatment for lesser increases in patients with cirrhosis or encephalopathy. Until the specific cause of abnormalities can be determined, clinicians should treat with at least three anti-TB agents that are less likely to cause hepatotoxicity namely streptomycin, Ethambutol and quinolones.

Rechallenge

The risk of reintroducing of a TB medication could be hazardous and should be considered relative to its potential benefit. Rechallenge is considered when it is unclear which medication was the cause of symptoms or of transaminases increases. Rechallenge also may be considered if an increase in transaminases concentration did not reach the usual treatment limiting threshold. Rechallenged patients who had reached a treatment limiting threshold should have clinical and biochemical monitoring at 2-to 4-week intervals. Rechallenged patients should be told to stop medication in case of hepatitis symptoms.

After the enzymes return to normal, the drugs are introduced sequentially. Isoniazid is introduced first at a dose of 50mg/day and increased to 300mg/day over the next 2-3 days if well tolerated.[2]

Rifampicin is introduced after another 3-4 days at doses of 75mg/day and increase to full dose over a period of 3-4 days. Pyrazinamide is introduced next at a dose of

250mg, increasing to 1000mg over the next few days.

Studies show that the recurrence of hepatotoxicity is very less after reintroduction of ATT. Singh et al reported a recurrence rate of 6.8% in their study. Telman et al reported a recurrence rate of 6.3%.[11]

A high recurrence rate was noted in one study in Copenhagen[10] (26%). Further multicentric studies are needed to clarify these issues.

AIMS AND OBJECTIVES

The aim of the study is to analyze the following-

1. To study the incidence of hepatotoxicity in patients taking antituberculous drug therapy under the RNTCP short course schedule in Madurai district

2. To analyze the various risk factors for development of hepatotoxicity.

MATERIALS AND METHODS

THE STUDY GROUP

The study was conducted on patients coming to the chest clinic in Govt. Rajaji hospital, Madurai. Approval from ethical committee was obtained. The study was a prospective study conducted for a period of one year between June 2007-2008.

The **inclusion criteria** were-

1. Patients prescribed to receive ATT for confirmed pulmonary or extra pulmonary tuberculosis under the RNTCP schedule.

2. Patients coming from in and around Madurai city, to minimize the rate of dropouts.

The **exclusion criteria** were-

1. Patients not receiving isoniazid or rifampicin as a part of therapy.

2. Patients with preexisting acute or chronic liver disease.

3. Patients with fatty liver as diagnosed by ultrasound examination of the abdomen.

4. Baseline transaminases more than twice the upper limit of normal.

5. Chronic alcohol intake.

6. Patients with previous history of hepatotoxicity due to ATT.

METHODS

All the patients had pretreatment evaluation clinically especially for evidence of liver disease, history of alcoholism or concomitant drug therapy and systemic illness in a prepared proforma, a copy of which is annexed. Baseline laboratory evaluation was done for all patients which included hemoglobin levels, serum albumin, liver function tests

and ultra sonogram of the abdomen and HIV status. Body mass index (BMI) was calculated as follows[2]-

BMI = weight (kg)/height (metre^2)

Malnutrition - <18.5kg/m^2

Normal – 18.5-24.9kg/m^2

Obese - ≥25kg/m^2

Normal values for LFT were as follows-

Serum albumin >3.5grams/dl – normal

Serum albumin <3.5grams/dl – hypoalbuminemia

Serum bilirubin 0.2-0.8 mg%--normal

AST 15-40 iu/l--normal

ALT 15-40 iu/l--normal

Anemia was defined as the hemoglobin of less than 13 g/dl in males and less than 12 g/dl in females.[22]

Mild anemia was defined as hemoglobin level of 10-12.9 g/dL in males and 10-11.9 g/dL in females, moderate anemia was defined as hemoglobin level of 7-9.9 g/dL and severe anemia was defined as hemoglobin level of less than 7g/dL both among males and females.[22, 23]

Viral markers were done to exclude chronic viral hepatitis at the start of therapy. Presence of fatty liver was excluded on the basis of ultrasonography.

The patients were categorized into various regimens in RNTCP according to the

type of disease, the details of which were explained previously.

Doses of the drugs were as follows-

Isoniazid-600mg

Rifampicin-450mg (600mg if >60kg)

Pyrazinamide-1500mg

Ethambutol- 1200mg

Every effort was taken to maintain compliance to the drug therapy.

Patients were informed about the side effects of medications and were asked to report immediately if they developed any of these symptoms. Patients with minor symptoms were treated symptomatically. Those with major symptoms suggestive of hepatotoxicity were hospitalized and evaluated.

Diagnosis of Drug Induced Hepatotoxicity:

Hepatotoxicity was defined as the presence of at least one of the following criteria:

(1) Appearance of jaundice.

(2) a rise of at least five times the upper limit of normal levels (40 IU/L) of serum aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) or >250IU/L on any one occasion without symptoms or more than three times ULN with symptoms.

(3) A rise in the level of serum total bilirubin > 1.5mg/dl.[24]

Liver enzymes (AST/ALT) were estimated using the UV kinetic International Federation of Clinical Chemistry method.

LFTs were repeated weekly for the first month then at the end of second month

and after the completion of ATT (six months).

If the patients developed evidence of hepatotoxicity, viral markers (hepatitis A, B, C) were again performed to rule out acute viral hepatitis.

The information collected regarding all the selected cases were recorded in a Master Chart. Data analysis was done with the help of computer using **Epidemiological Information Package (EPI 2002).**

Using this software, frequencies, percentages, means, standard deviations, chi square and ‘p’ values were calculated. Kruskul Wallis chi-square test was used to test the significance of difference between quantitative variables and Yate's test for qualitative variables. A 'p' value less than 0.05 is taken to denote significant relationship.

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RESULTS AND ANALYSIS OF OBSERVED DATA

EPIDEMIOLOGY

The study group was divided into various age groups which ranged between 15 and 78 years. A total of 166 patients were included in the study of which 156 patients were followed up till six months of treatment. Total number of dropouts from the study at the end of six months was 10 out of which seven patients dropped out at the end of two weeks and three at the end of three weeks. Most patients were from in and around Madurai city.

The mean age of the population was 36.6±13.8 years. Out of 156 patients, 88 were male (56.5%) and 68 were female (43.5%). Most of the patients were in the ages between 15 and 39 years (66%).

TABLE 3: AGE DISTRIBUTION OF PATIENTS

Age(yrs)	Male(M)	Female(F)	Total	%
<30	30	22	52	33.3
30-39	27	24	51	32.7
40-49	15	11	26	16.7
50-59	9	6	15	9.6
>60	7	5	12	7.7
MEAN			36.6 yrs	
S.D			13.8 yrs	

SYMPTOMATOLOGY

There was a higher proportion of pulmonary tuberculosis (n=90) than the extra pulmonary form (n=66). Pleural effusion was the most common form of extra pulmonary tuberculosis seen in 31 patients (19.9%) followed by neurotuberculosis in 16 patients (10%).

TABLE 4: SITE OF DISEASE

Site	M	F	Total	%
Pulmonary	50	40	90	57.7
Pleural effusion	20	11	31	19.9
Lymph node	5	8	13	8.3
Abdominal	2	2	4	2.6
Skeletal	2	0	2	1.3
NeuroTB	9	7	16	10.2

Ninety patients were registered under category I ATT (59%) followed by 52 patients in category III (32%) and 14 patients in category II (9%) as shown in table- 5.

TABLE 5: CATEGORY OF ATT

	M	F	T	%
Cat I	49	41	90	59
Cat II	10	4	14	9
Cat III	29	23	52	32

Eighty six patients were sputum positive (55%) out of which 56% were males and 44% were females.

TABLE 6: BODY MASS INDEX (BMI)

BMI	M	F	T	%
<18.5	20	15	35	22.4
18-24.9	59	47	106	68
>25	10	5	15	9.6
MEAN			20.5	
S.D			3.1	

The mean BMI was 20.5±3.1kg/m^2. Body mass index was <18.5kg/m^2 in 35 patients (22.4%).

The mean hemoglobin values were 10.4±1.8gms/dl. It was found that 49 patients (31.4%) had a hemoglobin level of <9.9grams/dl, signifying moderate to severe anemia.

TABLE 7: HEMOGLOBIN (Hb) LEVELS

Serum albumin levels were < 3.5 grams/dl in 37 patients (23.7%). The mean albumin values were 3.88±0.73grams/dl.

TABLE 8: SERUM ALBUMIN LEVELS

Albumin(grams/dl)	Cases	
	No.	%
< 3.5	37	23.7
> 3.5	119	76.3
Mean	3.88	
S.D.	0.73	

Nineteen patients (12%) had systemic disease in the form of diabetes mellitus or chronic renal failure.

Twenty two patients (14.1%) of patients tested positive for HIV.

RESULTS OF LFT

Overall, 24 patients out of 156 had some abnormality of liver function (15.4%). The most common form of hepatotoxicity was asymptomatic rise in transaminases (n=16) followed by acute hepatitis like picture with jaundice (n=8). All 16 patients who developed increase in enzymes were asymptomatic.

Eight patients developed jaundice. There was no incidence of fulminant hepatic failure or chronic hepatitis. All patients who developed liver injury were investigated for viral hepatitis and none of the patients tested positive for any of the viral markers performed namely, IgM antibody for HAV, HbSAg, and anti HCV. Most of the derangements occurred within the first two weeks of starting therapy and subsided spontaneously on stopping the drug within 4-6 weeks. The results are summarized in tables 9, 10 and 11.

TABLE 9: BILIRUBIN ABNORMALITIES

Bilirubin at	**< 1.5mg%**		**> 1.5mg%**		**Mean**	**S.D.**
	No.	**%**	**No.**	**%**		
0 week	156	100	-	-	0.81	0.19
2 weeks	150	94.9	6	5.1	1.01	0.37
4 weeks	154	98.7	2	1.3	0.85	0.19
24 weeks	156	100	-	-	0.78	0.16

It was observed that the mean bilirubin levels were 1.01±0.37mg% in the second week and dropped down to 0.85±0.19mg% at the end of four weeks. Six patients had jaundice at the end of two weeks and two patients had persistent jaundice at four weeks that recovered within the next two weeks.

The abnormalities in liver enzymes were analyzed in relation to the time of onset of enzyme elevation.

TABLE 10: ENZYME ABNORMALITIES

SGOT/SGPT at	NORMAL		INCREASED		Mean	S.D.
	No.	%	No.	%		
0 week	156	100	-	-	26.3	6.7
2 weeks	136	87.2	20	12.8	67.5	9.4
4 weeks	155	99.4	1	0.6	30.3	18.9
24 weeks	156	100	-	-	26.3	6.3

It was observed that most of the enzyme abnormalities occurred within the first 2 weeks. Twenty patients (12.8%) developed enzyme elevation within two weeks of starting therapy and only one patient had persisting abnormality at the end of four weeks.

The patterns of hepatotoxicity were analyzed in relation to symptoms and LFT abnormality.

TABLE 11: PATTERN OF HEPATOTOXICITY

Age group	Clinical hepatitis	Asymptomatic enzyme elevation		percentage
		Male	Female	
<30 yrs	1	1	3	25%
30-39	0	2	0	8.3%
40-49	3	4	0	29.16%
50-59	2	0	3	16.66%
>60	2	0	3	20.8%
total	8	7	9	

It was observed that asymptomatic enzyme elevation was the most common form of hepatotoxicity seen in 16 patients (66.6%) followed by clinical hepatitis with jaundice in eight patients (33.3%). There was near equal incidence of toxicity in males (n=7) and females (n=9).

The initial elevation in liver function tests is summarized in table 12.

TABLE 12: INITIAL ELEVATION OF LFTs

Weeks	No of patients	AST	ALT	Bilirubin
0	166	-	-	-
1	166	-	-	-
2	159	14	14	6
4	156	2	2	2
8	156	-	-	-
24	156	-	-	-
Total	156	16	16	8
Values indicate number of patients.				

Analysis of hepatotoxicity in relation to the various risk factor parameters was done and the following observations were made-

1. <u>Category of ATT</u>:

It was observed that six patients (42.9%) started on category II developed toxicity in comparison to 13 patients (14.4%) on category I and five patients (9.6 %) on category III.

TABLE 13: CATEGORY OF ATT VERSUS HEPATOTOXICITY

Category of ATT	**LFT abnormality**			
	Present		**Absent**	
	No.	**%**	**No.**	**%**
I (90)	13	14.4	77	85.6
II (14)	6	42.9	8	57.1
III (52)	5	9.6	47	90.4

2. **Age group**:

It was observed that five out of 12 patients above the age of 60 years developed abnormalities of LFT (41.7%).

TABLE 14: AGE AND HEPATOTOXICITY

The value was statistically significant **(p=0.0027),** implying that the elderly patients were more susceptible to liver damage due to ATT.

3. **Sputum positivity**:

It was observed that out of 86 patients who were sputum positive, 19 developed hepatotoxicity (22.1%) in comparison with only five sputum negative patients (7.1%).

TABLE 15: SPUTUM POSITIVITY VERSUS HEPATOTOXICTY

Sputum	**LFT abnormality**			
	Present		**Absent**	
	No.	**%**	**No.**	**%**
Positive (86)	19	22.1	67	77.9
Negative (70)	5	7.1	65	92.9
'p'	**0.0187** **Significant**			

80% of patients with hepatotoxicity were sputum positive, possibly indicating severe disease as a risk factor for hepatotoxicity. The value was statistically significant **(p=0.0187).**

4. **Hemoglobin**:

Out of 49 patients who had moderate to severe anemia, 17 developed liver injury (34.7%). In contrast, only seven patients who had hemoglobin levels above 9.9grams% developed toxicity (6.5%).

TABLE 16: ANEMIA VERSUS HEPATOTOXICTY

70% of patients with toxicity had hemoglobin levels <9.9gm% and the value was statistically significant **(p=0.0001).** Moderate to severe anemia directly correlated with hepatotoxicity.

5. **Body mass index:**

It was observed that 19 out of 35 patients (54.3%) with BMI <18.5kg/m^2 had LFT abnormalities.

TABLE 17: MALNUTRITION AND HEPATOTOXICITY

BMI (kg/m^2)	**LFT abnormality**			
	Present		**Absent**	
	No.	**%**	**No.**	**%**
≤18.5 (35)	19	54.3	16	45.7
> 18.5 (121)	5	4.1	116	95.9
Mean	17.13		21.09	
S.D.	1.39		2.9	
'p'	**0.0001** **Significant**			

80% of patients with toxicity had BMI values of <18.5kg/m^2 and the value was statistically significant **(p=0.0001),** implying that malnutrition may be a significant risk factor for toxicity.

6. **Serum albumin**:

It was observed that 45.9% of patients with hypoalbuminemia (n=17) had toxicity. The value was statistically significant (**p=0.0001**) as shown in the table below.

TABLE 18: HYPOALBUMINEMIA AND HEPATOTOXICITY

Serum albumin (grams/dl)	**LFT abnormality**			
	Present		**Absent**	
	No.	**%**	**No.**	**%**
≤ 3.5 (37)	17	45.9	20	54.1
> 3.5 (119)	7	5.9	112	94.1
Mean	3.14		4.01	
S.D.	0.84		0.61	
'p'	**0.0001** **Significant**			

7**. <u>HIV status:</u>**

Out of 22 patients who tested positive for HIV, 11 (50%) developed hepatotoxicity.

TABLE 19: HIV STATUS AND HEPATOTOXICITY

HIV	LFT abnormality			
	Present		Absent	
	No.	%	No.	%
Positive (22)	11	50	11	50
Negative (134)	13	9.7	121	90.3
'p'	**0.0001** **Significant**			

The value obtained was statistically significant **(p=0.0001)** indicating that HIV infection may be a significant risk factor for ATT induced hepatotoxicity.

8. **<u>Site of disease</u>**:

Hepatotoxicity was more in abdominal (25%) and pulmonary tuberculosis (22.2%) that in other types of tuberculosis.

TABLE 20: SITE OF DISEASE AND HEPATOTOXICITY

Site of disease	LFT abnormality			
	Present		Absent	
	No.	%	No.	%
AB (4)	1	25	3	75
LN (13)	-	-	13	100
P (90)	20	22.2	70	77.8
PE (31)	3	9.7	28	90.3
SK (2)	-	-	2	100
TBM (16)	-	-	16	100

DISCUSSION

The wide prevalence of tuberculosis through out the world makes it a social and economical burden especially for developing countries and the use of anti tuberculous drugs is an optimistic approach for this problem. However certain reservations associated with its use need to be properly evaluated especially ATT induced liver injury and the predisposing factors that add to this hepatotoxicity.

This study was conducted to study the incidence of ATT induced hepatotoxicity in RNTCP clinic, Madurai and to assess the role of age, sex, severity of the disease, nutritional status, hypoalbuminemia, sputum positivity and HIV status as risk factor for ATT induced hepatotoxicity.

The reported incidence of ATT induced hepatotoxicity is different in various countries though not fully understood but could be due to the characteristics and the risk factors of the population studied, the different diagnostic criteria used to define hepatotoxicity, different geographical areas, tests carried out during follow ups and the type of monitoring.[25]

Why only some patients who receive ATT develop hepatitis is not clear and several studies searched for host factors, environmental factors or some interaction among various factors. While some papers have focused on genetic factors, such as HLA typing, Cytochrome P450 2E1 or acetylator status, others have primarily studied clinical factors.

In this study of 156 patients, all were administered DOTS therapy under RNTCP

and belonged to different treatment categories. Male: female ratio was almost equal (53.5%:48.5%). Age group of the patients ranged from 15-78 years.

Various studies report different incidence rates of hepatotoxicity due to anti tuberculous therapy. A higher risk of hepatotoxicity has been reported in Indian patients than in their Western counterparts.[19, 26] the risk of hepatotoxicity based on data from four prospective Indian studies was 11.5% compared with 4.3% in Western publications.[15]

In our study 15.4% of the patients developed ATT induced hepatotoxicity that almost overlaps the other studies conducted world wide. The incidence of hepatotoxicity due to combination chemotherapy ranges from 1-39%. The following is a list of incidence by some workers:

1. Parthasarathy et al [27] TBM: 16-39%, PT: 2-3%
2. Schberg et al [9] 11%
3. Devoto et al [21] 9.9%
4. Steele et al [15] 2.6%
5. Dossing et al [10] 8%
6. Kamat et al[28] 18%
7. Sivaraman et al[29] 7%
8. Our study 15.4%

The TRC, Chennai published its first report on hepatotoxicity induced by antituberculous drug therapy and the incidence was 2.5%.

In a study done in Pakistan, 19.76% of the patients developed ATT induced hepatotoxicity that almost overlapped the study conducted at Japan.[30,31] A study conducted in Nepal[32] resulted in 8% and 13% in Hong Kong Chinese patients.[33] In the analysis done by Col AC Anand et al, the incidence of hepatotoxicity among patients on ATT was 10.1%,[34]

In our study we analyzed the possible predisposing factors for hepatotoxicity induced ATT. A significant proportion of patients older than 60 years developed hepatotoxicity (p=0.0027). Although the number of patients above the age of 60 years receiving ATT was less (n=12), nearly half of these patients developed liver function abnormalities.

Some studies have reported that the risk of ATT-induced hepatitis increases with advancing age, the highest incidence being in individuals older than 50 years as shown by Gangadharan et al.[35]

In a study done by Col AC Anand et al in 2006, no significant correlation of age with ATT-induced hepatotoxicity was found. However, once hepatotoxicity developed, fatal out come was much more likely among the older patients (mean age 47.1 years as compared to 38.9 years in non fatal cases).[34] Studies from Pande et al and other workers showed that increasing age is associated with more hepatotoxicity.[20, 36, 37]

In a study done by Khalid Mohammad et al, older age group was affected more as compared to younger one (25.8% vs. 14.4%).[30]

Although previous studies have quoted an increased risk of hepatotoxicity for females, it was found to be almost equal in this study. There was a marginal increase in sub clinical hepatitis in females in accordance with many other studies (nine in females vs. seven in males). Vulnerability of females could be due to variations in pharmacokinetics and slow acetylating enzymatic pattern, resulting in hepatotoxicity.[20, 38]

Anand AC et al did not find any difference in the incidence of hepatotoxicity in their study.[34] This has also been reported in a study done by Taneja et al.[39]

Nutritional status of our patients was very poor. BMI were below 18.5 (kg/m2) in 23% of patients and 23.4% of the patients had hypoalbuminemia. In our study there was a significant relationship of hepatotoxicity to low serum albumin and low BMI as noted in the previous studies done by Pande et al[20]. Nearly 72% of patients with hepatotoxicity had serum albumin <3.5 grams%.

Krishnasamy says that under nutrition contributes to drug toxicity by various mechanisms. [40, 41] Toxicity and over dosage is much more likely to occur even with normal dosage of medicine in the presence of normal serum albumin.[42] A study from Pakistan shows significant correlation between the two variables.[30]

The possible explanation of ATT induced hepatotoxicity in malnutrition is depletion of glutathione stores that makes one vulnerable to oxidative injuries. Low

nutritional status is considered to be one of the factors contributing to relatively high incidence of ATT-related hepatitis in studies from developing countries. Drug metabolism pathways including acetylation pathway have been shown to be deranged in states of protein energy malnutrition.[43, 44]

A direct correlation was also obtained between low BMI and hepatotoxicity (p=0.0001) and this was in concordance with the previous studies done by Shakya et al.[7] A similar significant relationship was noted between hemoglobin levels and hepatotoxicity (p=0.0001). Most of the patients with hepatotoxicity had severe anemia.

Nineteen patients (80%) were sputum smear positive and they were severely affected indicating the extensiveness of the disease also as a risk factor as noted in previous studies done by Pande et al[20] (p=0.001)and Devoto et al [21](p=0.02). Severity of the disease in sputum smear positive patients could be secondary to more tubercular bacilli in smear positive patients as compared to smear negative patients.

In our study, there was direct association between sputum positivity and hepatotoxicity (p=0.0187). In the study done by Khalid Mohammad, forty patients (59.70%) were sputum smear positive and they were severely affected indicating the extensiveness of the disease as a risk factor.[30, 45, 10, 20]

In our study, HIV infection was found to be a significant risk factor for TB DILI (p=0.0001). The patients were not on antiretroviral therapy at the start of ATT, thus ruling out antiretroviral therapy as the cause of liver function abnormalities. This was in concordance with the previous studies done by the European tuberculosis study group

where it was found that patients with HIV and TB had significant risk of hepatotoxicity irrespective of whether the patient was on ART or not.[16]

None of the patients in this study who developed toxicity had viral hepatitis though there is evidence to indicate that patients with viral hepatitis B or hepatitis C had a higher risk of drug toxicity than general population.[46, 47, 48]

The frequency of self limiting asymptomatic enzyme elevation raises the question of whether the drugs should be stopped; and if so, at what levels they should be stopped. Mild transient self limiting transaminase rise occurs early during the course of therapy irrespective of the regimen used and this should not be used as a criterion for stopping therapy. Onset of hepatotoxicity occurred within one month of start of therapy in our study. Usually pyrazinamide produced a delayed onset of hepatotoxicity whereas early toxicity is produced by isoniazid and rifampicin.

Parthasarathy et al concluded that acute hepatitis is nearly always associated with jaundice.[27] In our study also, patients who developed jaundice has an enzyme elevation of >200 IU/L. after withdrawing the drugs, all levels returned to normal within four weeks.

Some workers say it may not be advisable to stop all drugs at a time but since the possibility of fulminant hepatic failure always arises, it is advisable to stop all drugs till enzyme elevation settles down to normal levels. In our study, all drugs were

reintroduced according to the British Thoracic society guidelines[24]. None of the patients developed recurrent hepatotoxicity.

The onset of drug induced hepatotoxicity cannot be exactly predicted but measures to prevent it can be taken well in advance. High protein diet, abstinence from alcohol and smoking, good supportive medications like vitamin B6 and vitamin C have shown to reduce the incidence of hepatotoxicity. Well educated patients and skilled, alert, treatment supervisor can reduce the hepatotoxicity, fulminant hepatitis and its complications.

SUMMARY

In this study, 156 patients belonging to different categories of RNTCP-DOTS were followed up for a period of six months. There were 88 Males and 68 females. 15.4% of patients developed liver function abnormalities of which asymptomatic enzyme elevation was the most common feature. There was no incidence of fulminant hepatic failure or chronic hepatitis.

Transient self limiting rise of transaminases occurred early during the course of therapy which subsided on stopping drug over a period of four to six weeks. Reintroduction of ATT was tolerated well and all had completed treatment. Advancing age, malnutrition, anemia, advanced disease with sputum positivity, hypoproteinemia and HIV positivity directly correlated with drug induced hepatotoxicity.

Identification of these risk factors may be helpful in predicting hepatotoxicity and correction of the modifiable risk factors prior to start of therapy may prevent liver damage.

CONCLUSIONS

The following conclusions were made from our study-

1. Liver function abnormalities occurred in 15% of the study group under

RNTCP which is a significant number.

2. Asymptomatic enzyme elevation is the most common abnormality in our study.

3. Direct correlation existed between increasing ages, malnutrition, anaemia, advanced disease with sputum positivity and hypoproteinemia.

Correction of the modifiable risk factors can lead to decrease in hepatotoxicity.

4. Hepatotoxicity is usually self limiting and treatment need not be discontinued permanently.

5. Serial monitoring of liver function tests will help in early identification of drug induced hepatotoxicity and prevention of fulminant hepatic failure.

6. Further research is needed to find out the exact mechanisms of hepatotoxicity due to ATT and the possible role of hepatoprotective agents.

FIGURE 1

Illustration of the proposed mechanism of DILI, which involves drug metabolism, hepatocyte damage, activation of innate immune cells, and production of tissue-damaging and tissue-protective mediators. CYP - cytochrome P450; IFN- interferon; IL- interleukin; NK-natural killer cell; NKT- natural killer T cell; TNF- tumor necrosis factor.

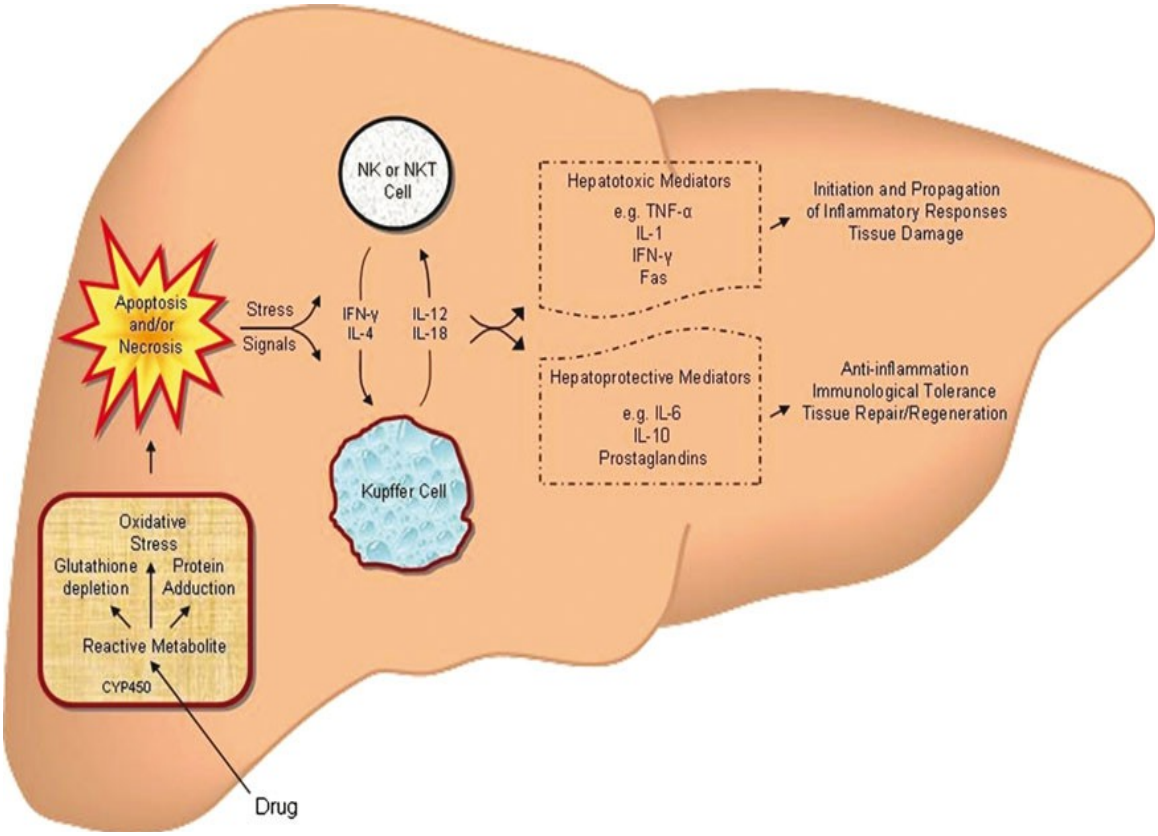


FIGURE 2: AGE DISTRIBUTION

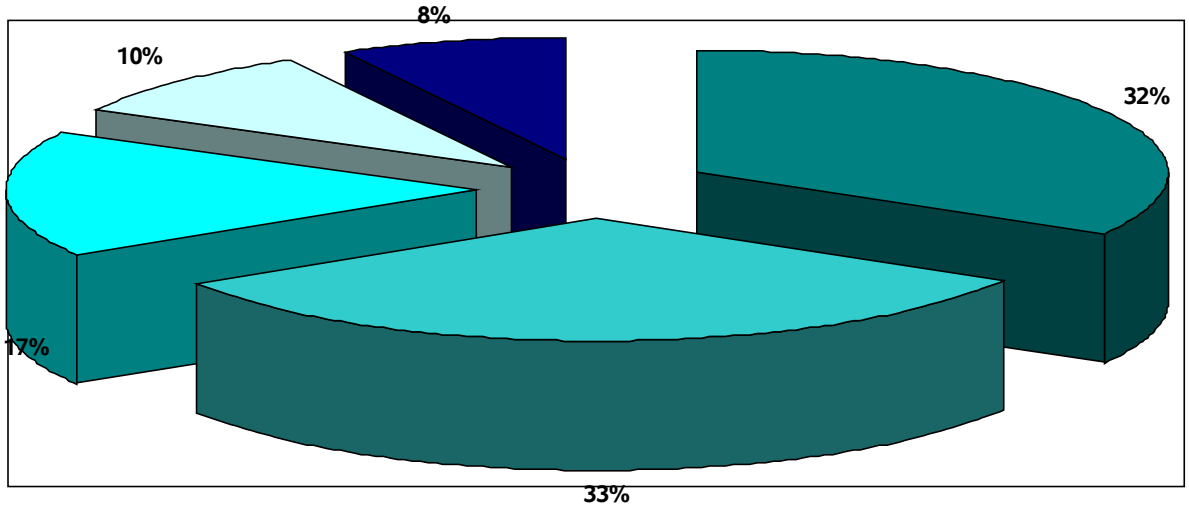
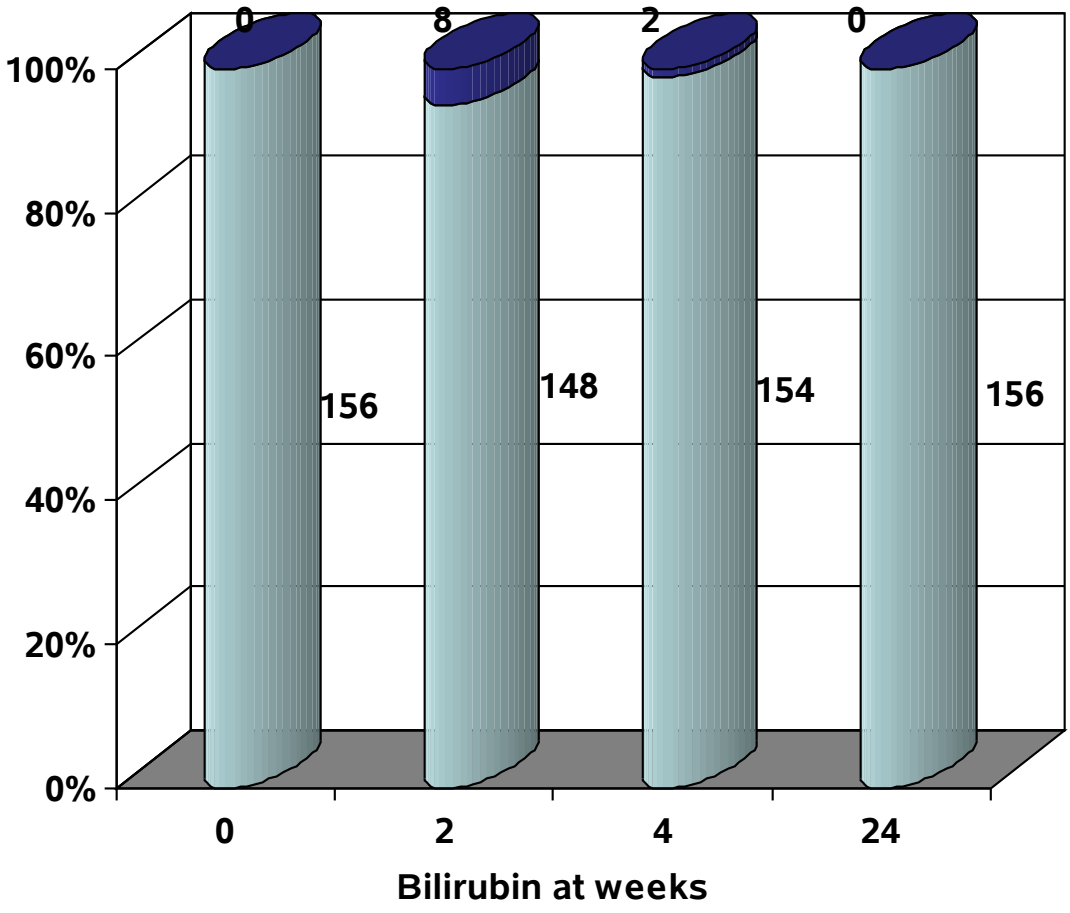

8%
10%
32%
17%
33%
Less than 30
30-39
40-49
50-59
60 & above

FIGURE 3: BILIRUBIN ABNORMALITIES



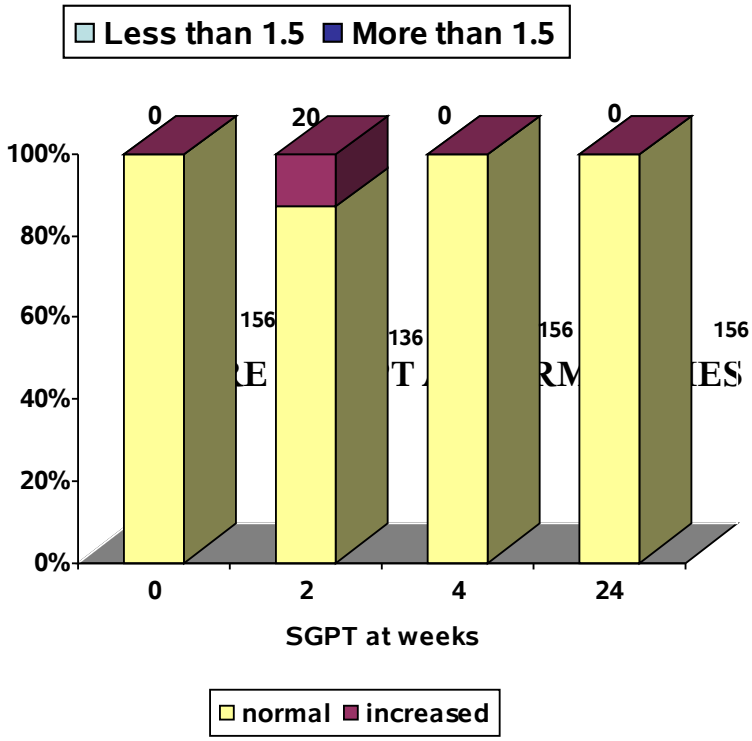


FIGURE 5: SGOT ABNORMALITIES

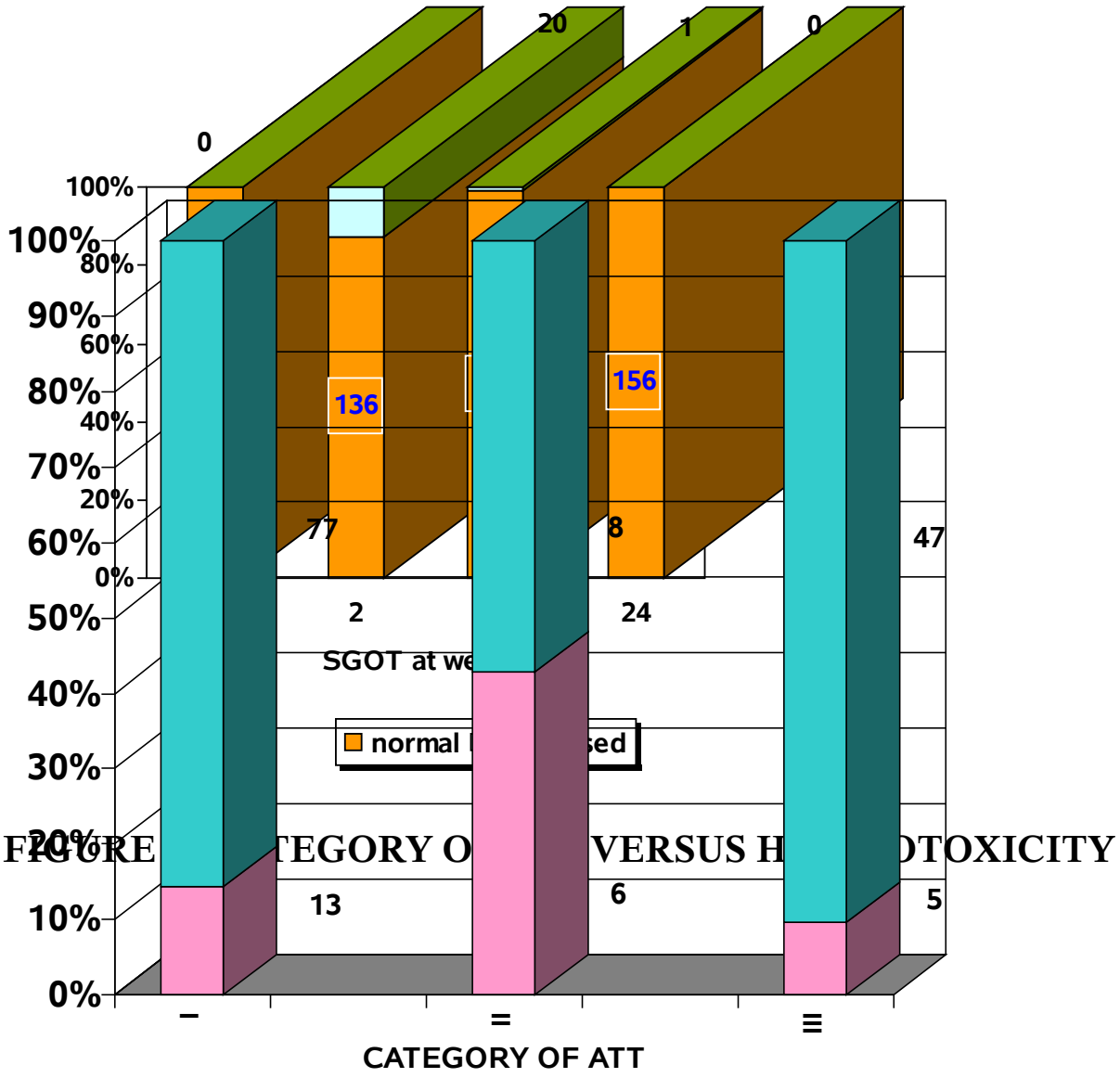
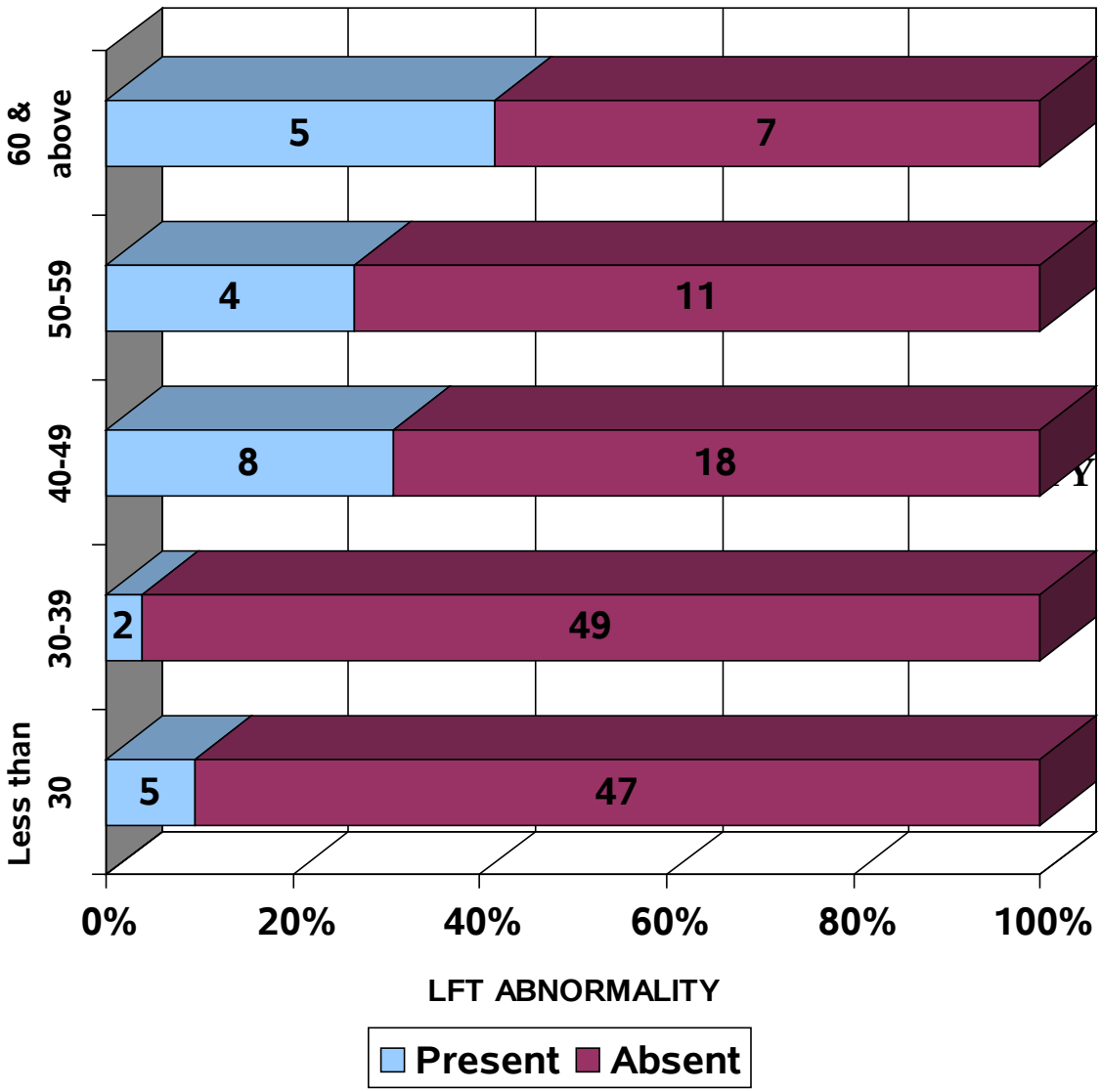


FIGURE [illegible]TEGORY O[illegible]VERSUS H[illegible]OTOXICITY


60 & above
50-59
40-49
30-39
Less than 30
5
7
4
11
8
18
2
49
5
47
0%
20%
40%
60%
80%
100%
LFT ABNORMALITY
Present
Absent

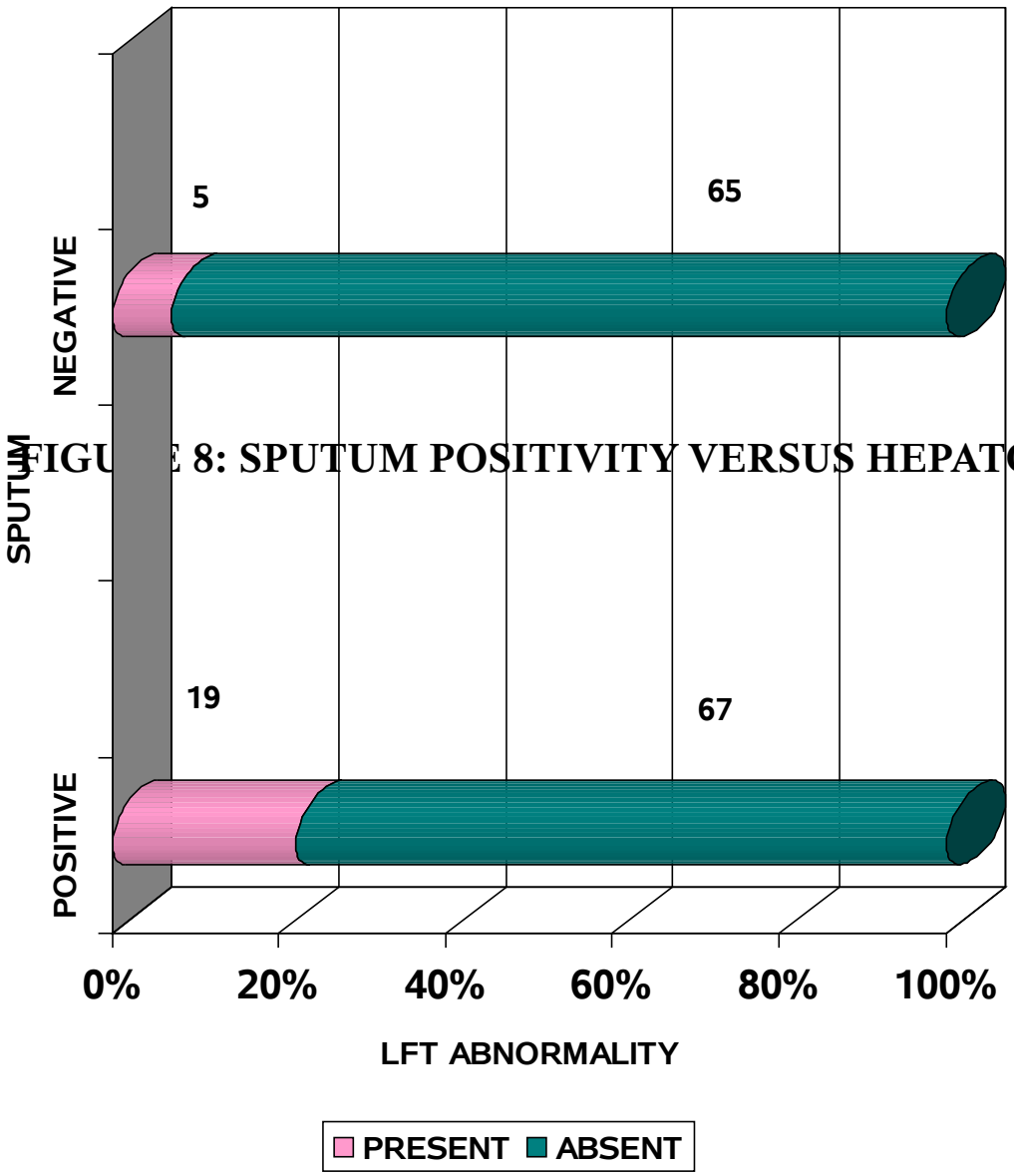


FIGURE 8: SPUTUM POSITIVITY VERSUS HEPATOTOXICITY

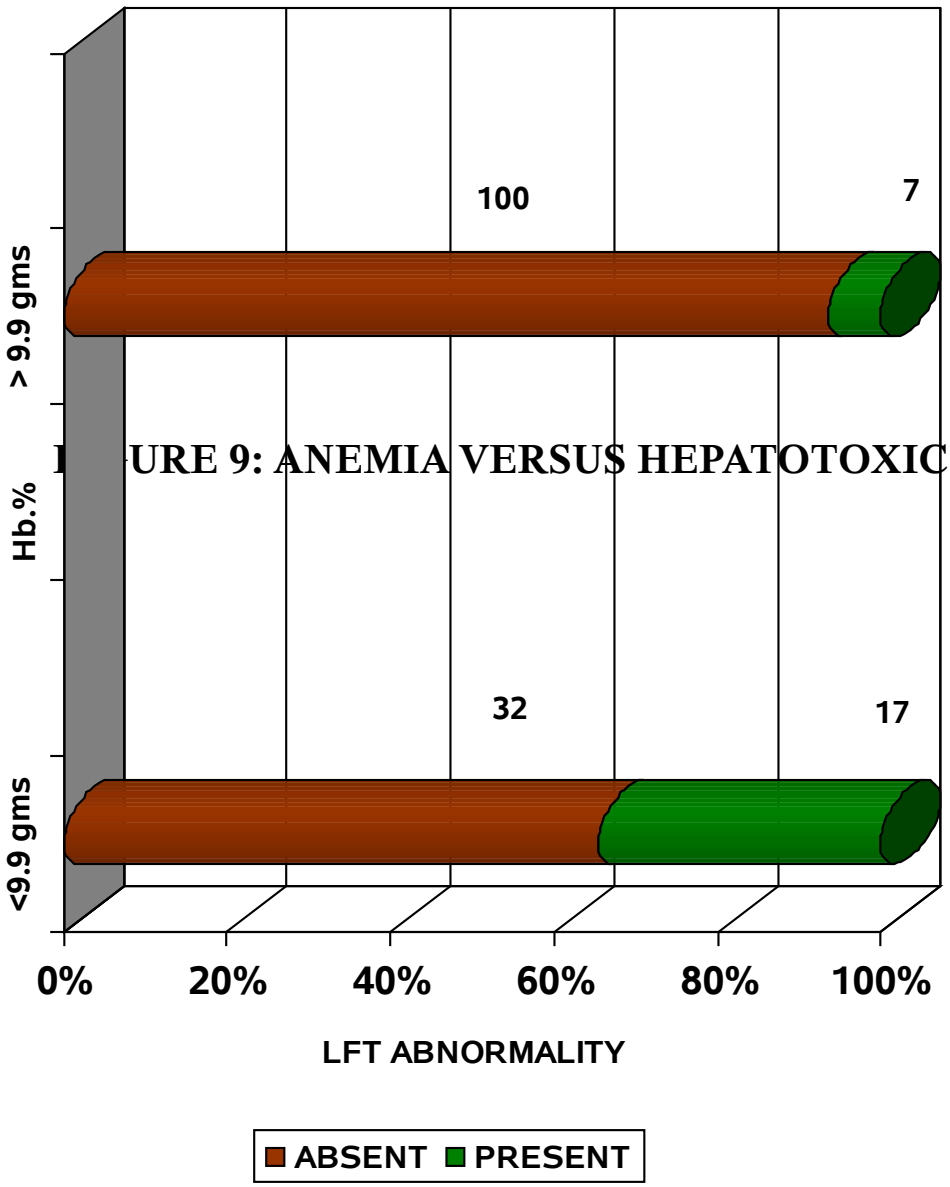


FIGURE 9: ANEMIA VERSUS HEPATOTOXICITY

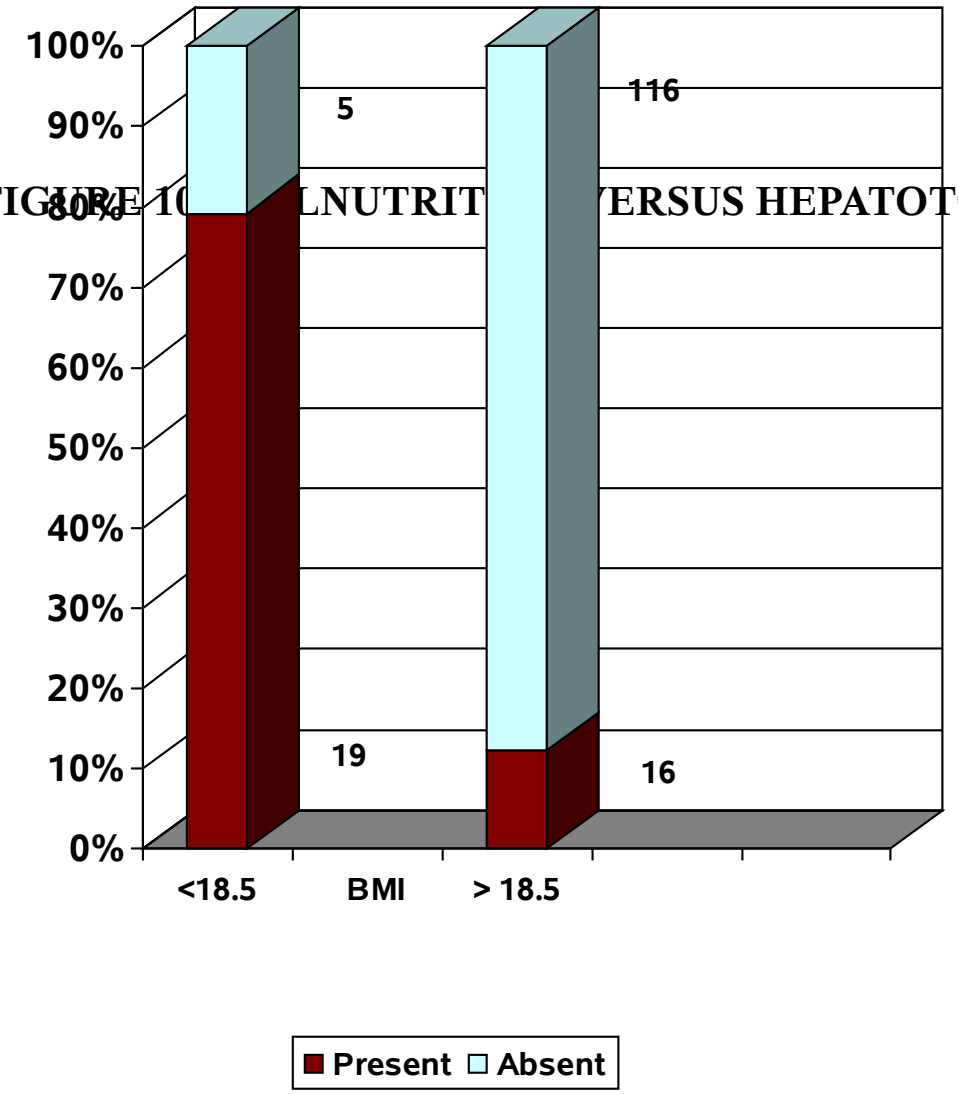


FIGURE 10 LNUTRIT VERSUS HEPATOTOXICITY

FIGURE 11: HYPOALBUMINEMIA VERSUS HEPATOTOXICITY

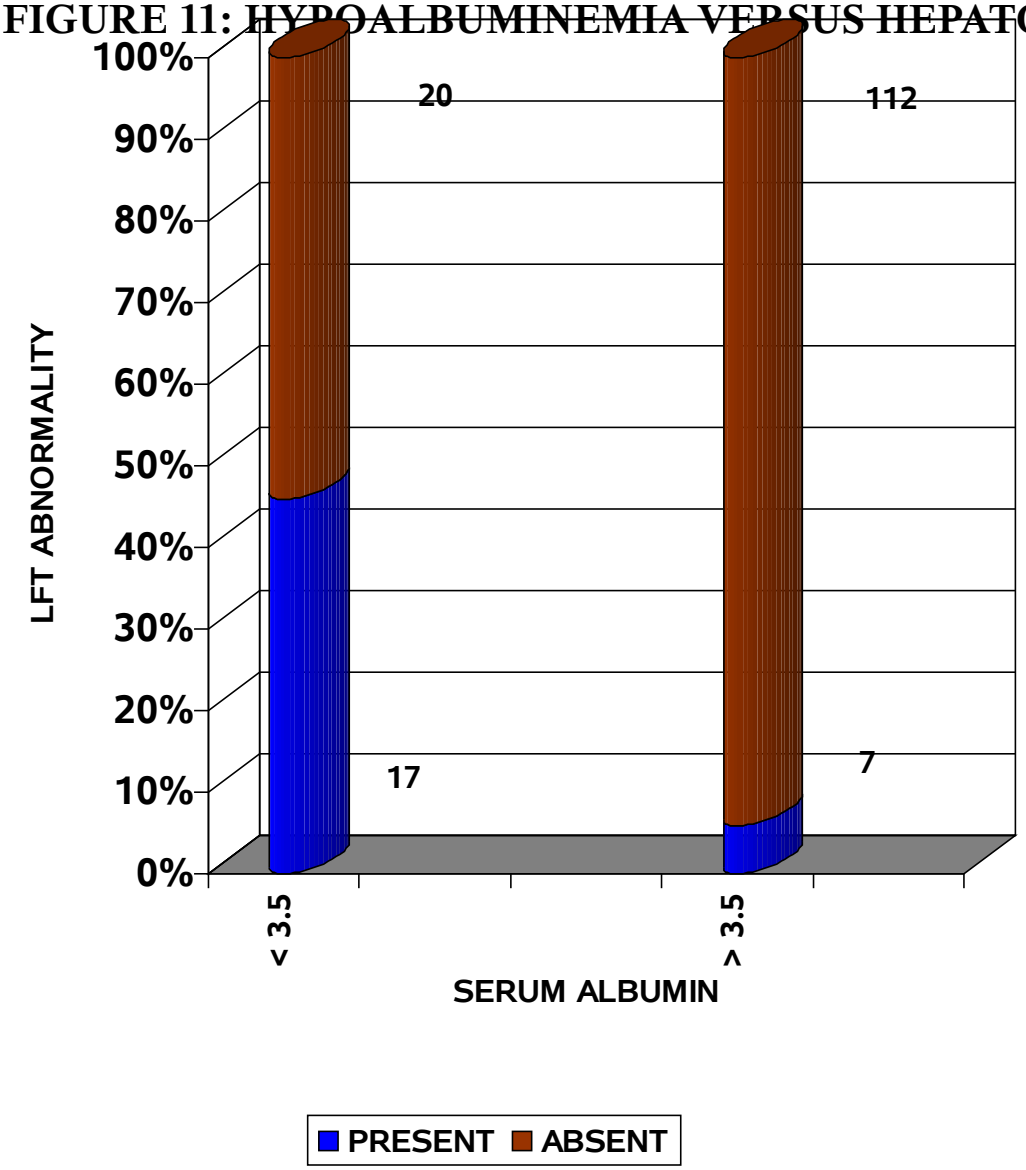
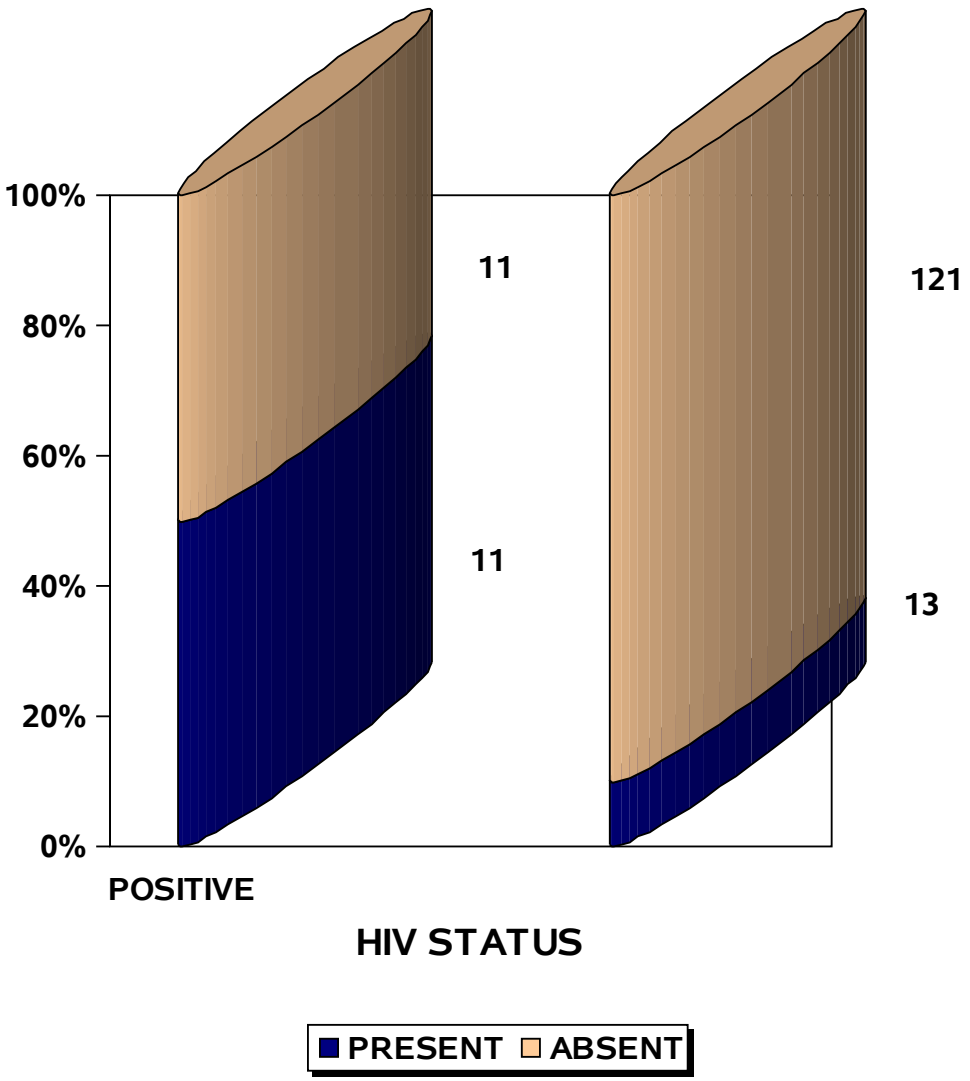


FIGURE 12: HIV STATUS VERSUS HEPATOTOXICITY



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PROFORMA

S.NO
NAME: AGE: SEX: M/F
ADDRESS: IP/OP NO.:

DIAGNOSIS: P/PE/LN/TBM/AB/SK RNTCP CATEGORY: I
II
III

SPUTUM +/-
DATE OF STARTING ATT:

SYMPTOMS	ONSET	DURATION
ANOREXIA		
NAUSEA		
VOMITING		
JAUNDICE		
BLEEDING		
FEVER		
JOINT PAIN		
CLAY STOOLS		
RASH		
EPIGASTRIC PAIN		

CLINICAL EXAMINATION

WEIGHT	HEIGHT
BMI	ANEMIA
JAUNDICE	HEPATOMEGALY
RIGHT HYPOCHONDRIAL TENDERNESS	
SKIN RASH	
ARTHRITIS	BLEEDING

INVESTIGATIONS

HEMOGLOBIN

TOTAL WBC COUNT

DIFFERNTIAL COUNT

PERIPHERAL SMEAR

URINE BILE SALTS

URINE BILE PIGMENTS

URINE ALBUMIN

CHEST X RAY PA VIEW

HIV ELISA

ULTRASONOGRAM ABDOMEN

LIVER FUNCTION TESTS:

IgM Anti HAV

HBsAg

AntiHCV

PARAMETER	WEEK					
	0	1	2	4	8	24
S.BILIRUBIN TOTAL DIRECT INDIRECT						
SGOT						
SGPT						
ALP						
S.PROTEINS TOTAL ALBUMIN GLOBULIN						

KEY TO MASTER CHART

PT ID - patient identification

BMI - body mass index

HB - hemoglobin

AST - aspartate transaminase

ALT - alanine transaminase

HIV - human immunodeficiency virus

P - Pulmonary

PE - pleural effusion

AB - abdominal

TBM - tuberculous meningitis

SK - skeletal

LN - lymph node

m - Male

f- Female

dm – diabetes mellitus

crf – chronic renal failure

+ Positive

- Negative

ABBREVIATIONS

AB – Abdominal

AIDS – Acquired Immuno Deficiency Syndrome

AIIMS - All India Institute of Medical Sciences

ART – Anti Retroviral Therapy

CSF – Cerebrospinal fluid

DOTS – Directly Observed Treatment Short Course

HAV - Hepatitis A virus

HBeAg – Hepatitis B e Antigen

HBsAg – Hepatitis B surface Antigen

HCV – Hepatitis C virus

HIV - Human Immunodeficiency Virus

HLA – Human Leucocyte Antigen

IFN – Interferon

INH – Isoniazid

LFT – Liver Function Tests

LN – Lymph node

MDR – Multi Drug Resistant

P – Pulmonary

PE – Pleural effusion

SGOT – Serum Glutamate Oxaloacetate Transaminase

SGPT – Serum Glutamate Pyruvate Transaminase

SK – Skeletal

TB – Tuberculosis

TBM – Tuberculous meningitis

TRC - Tuberculosis Research Center

ULN – Upper Limit of Normal

WHO - World Health Organization